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ORIGINAL ARTICLES

Magnetic Resonance Imaging Evaluation of Aortic Elastic Properties as Early Expression of Marfan Syndrome

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ABSTRACT

In Marfan syndrome, early identification and treatment of aortic involvement could improve prognosis, but clinical diagnosis may be difficult at a young age, before aortic dilation occurs. The aim of this study was to evaluate biomechanical aortic properties in Marfan patients and in their relatives to identify an early index of aortic involvement. A magnetic resonance imaging (MRI) morphologic and functional study of the thoracic aorta was performed in 20 Marfan patients, 15 family members, and 14 healthy volunteers as a control group. The aorta was imaged in the oblique sagittal plane by spin-echo sequence. A high-resolution gradient-echo sequence was then applied in the axial plane at the level of ascending supravalvular aorta to evaluate aortic distensibility. Aortic distensibility (mm Hg^{-1}) was significantly different in the three groups (ANOVA, $p = 0.0001$). Aortic distensibility was sensibly reduced in Marfan patients (0.0085 ± 0.006 vs. 0.025 ± 0.006 control group, $p < 0.05$). No significant correlation was found between aortic area and distensibility. Aortic distensibility was reduced also in family members (0.016 ± 0.011 vs. 0.025 ± 0.006 control group, $p < 0.05$). Among them, 4 subjects showed aortic diameters to the upper limit of the normal range, whereas the other 11 presented normal aortic diameters. Intraobserver and interobserver reproducibility for diastolic measurement was 1.2% and 0.4%, respectively, and 1.1% and 0.3%, respectively, for systolic measurement. MRI is an accurate technique in detecting abnormal aortic elastic properties in Marfan patients. Abnormal ascending aorta distensibility may constitute an index of early aortic involvement before dilation occurs.

KEY WORDS: *Aorta; Aortic elastic properties; Magnetic resonance imaging; Marfan syndrome.*

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INTRODUCTION

Marfan syndrome is a connective tissue disorder with autosomal dominant inheritance and a prevalence of at least 1:3000/5000 (1–3). In approximately 25–30% of cases, new mutation is continued that suggests parental germline defect (4). Because of the disease's wide and variable clinical manifestations, diagnosis of Marfan syndrome is based on the assessment of major and minor criteria established by the recently revised Ghent Nosology (1). The cardiovascular complications associated with Marfan syndrome reduce patients' life expectancy by one third, on average (3,5). Progressive aortic dilation with subsequent dissection or rupture is the leading cause of death. However, though the monitoring of aortic diameters is mandatory, such parameters are not always reliable as dissection can occur also without aortic dilation (6,7).

Prognosis could be significantly improved by early diagnosis and prophylactic surgical repair, because mortality is much higher when surgery is performed as an emergency procedure (6). Unfortunately, most clinical criteria are age dependent and do not usually suffice as grounds for early diagnosis.

In Marfan syndrome, structural abnormalities causing aortic dilation and dissection are also manifested by abnormal elastic properties. It has been demonstrated that magnetic resonance imaging (MRI) is the most accurate tool in the evaluation of aortic pathology, providing both precise morphologic information and functional characteristics. Previous studies have demonstrated MRI's ability to detect abnormal aortic compliance and distensibility in Marfan patients (8–13).

The aim of this study was to evaluate aortic biomechanical properties in Marfan patients and their relatives to identify an early index of aortic involvement.

METHODS

Twenty patients who fulfilled the diagnostic criteria of Marfan syndrome (10 men and 10 women, aged 10–42 yr, mean age 27.8 ± 9.2 yr), 15 relatives of Marfan syndrome patients (10 men and 5 women, aged 6–24, mean age 14.7 ± 6.2 yr), and a control group of 14 healthy volunteers (7 men and 7 women, aged 25–32, mean age 29 ± 3.0 yr) were studied. All the family members presented isolated Marfan features, but none of them fulfilled the diagnostic criteria (1). Beta-blocker therapy or other medication that could interfere with aorta measurements was stopped 24 hr before the MRI examination.

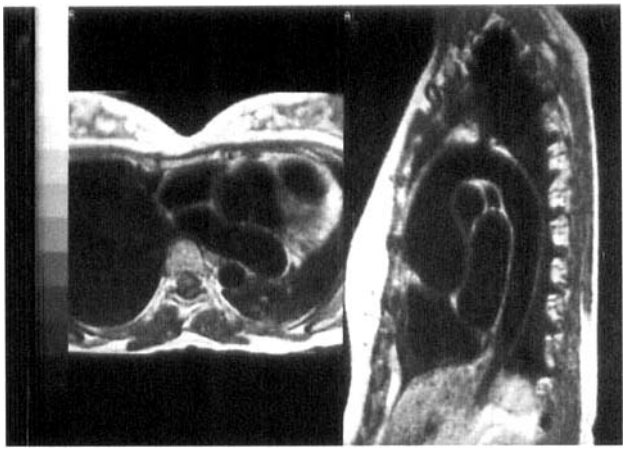

Figure 1. Axial and sagittal spin-echo images of the thoracic aorta in a Marfan patient. A moderate enlargement of the ascending aorta is visible.

An MRI examination was performed in all subjects. The study included morphologic and functional evaluation. A multislice spin-echo study (TE 20 msec, TR according to RR interval of electrocardiogram) of the thoracic aorta was performed in the axial and sagittal plane (Fig.1). The functional study consisted of a single-slice gradient-echo sequence (TR 25 msec, TE 17 msec, flip angle 35 degrees, slice thickness 7 mm, matrix 256 × 256, field of view 35 mm, four number of excitations) on the axial plane of the ascending supravalvular aorta taken perpendicularly to the mid-ascending and descending aorta at pulmonary artery level (Fig. 2). The diastolic images were acquired 10 msec after the R wave, and the systolic images were acquired after the electrocardiogram T wave. Acquisition time was 8–12 min per image depending on heart rate.

Aortic distensibility (mm Hg^{-1}) was calculated according to the following formula (14): distensibility = 2 (aortic luminal area change)/(diastolic luminal area × pulse pressure).

The aortic lumen was outlined manually on the computer screen to measure the aortic area (Fig. 2). Measurements were repeated on three occasions by two operators blind to each other's results. An average of the measurements was taken. The aortic diameter was then measured on the MRI axial plane. Arterial blood pressure was measured using the auscultatory method with sphygmomanometer on the left arm both before and after the respective images were acquired, and pulse pressure was

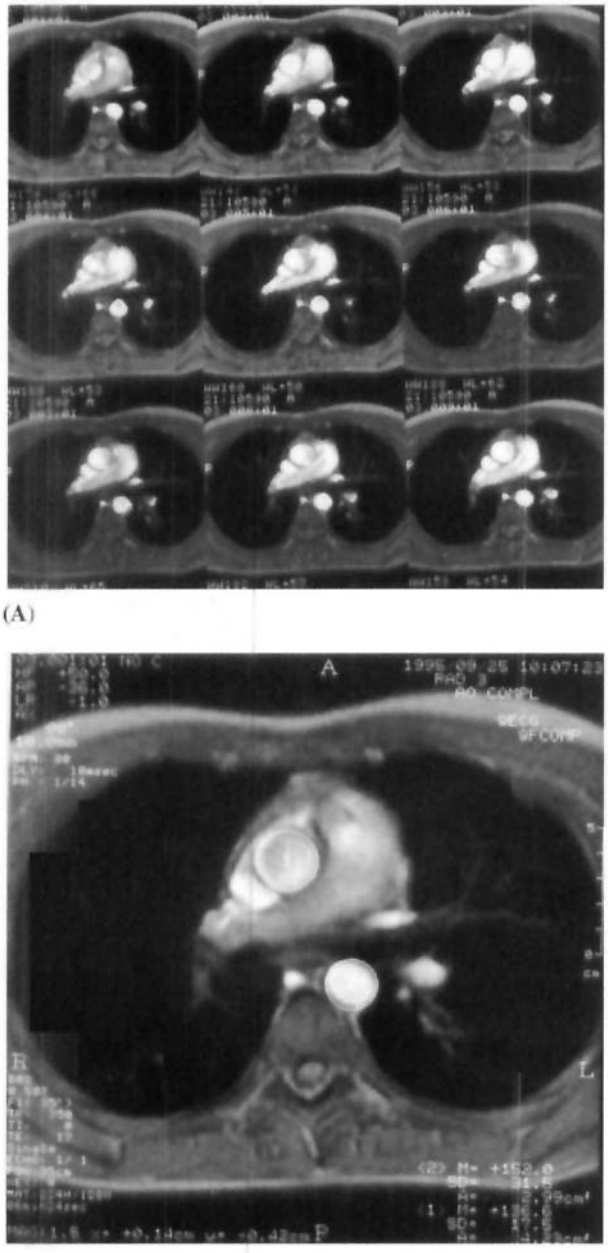

Figure 2. Axial gradient-echo image of the thoracic aorta in a 16-year-old family member. Systolic and diastolic images of the mid-ascending aorta lumen are used to measure the aortic area on a computer screen. (A) Systolic image of the mid-ascending aorta: The aortic lumen is outlined on the computer screen to measure the aortic area (B).

calculated as the difference between systolic and diastolic blood pressure.

To assess the effectiveness of the measurements of aortic distensibility, intraobserver and interobserver reproducibility was calculated as the standard deviation of the differences of measurements expressed as a percentage of the mean of the measurements (15). ANOVA and Bonferroni t-test for pairwise comparisons were used for statistical evaluation; $p < 0.05$ was considered statistically significant.

RESULTS

As far as demographic characteristics and body surface area were concerned, there was no difference in age or gender distribution between the Marfan patients and the control group, although the subjects in the Marfan group had larger body surface area values (1.9 ± 0.23 m^2 Marfan group, 1.73 ± 0.20 m^2 family members, 1.70 ± 0.08 m^2 control subjects, $p < 0.05$). Systolic, diastolic, and pulse pressure values; ascending aortic areas (absolute value and normalized to body area); and ascending aorta distensibility for Marfan, control, and family members groups are shown in Table 1.

Systolic, diastolic, and pulse pressures and ascending aortic area were not significantly different between the three groups. The aortic distensibility of ascending aorta was significantly reduced in the Marfan patients compared with the control group (Fig. 3). No significant relationship between aortic area and distensibility was found in Marfan patients (Fig. 4). Despite their young age, several family members presented reduced aortic distensibility. Of this subset, 1 family member presented slight aortic dilation, 3 presented aortic diameters at the upper limits of normal values, and 11 had normal aortic diameters.

Intraobserver reproducibility ranged from 1.2% for the ascending aorta in diastole to 1.1% for the ascending aorta in systole. Similarly, interobserver reproducibility ranged from 0.4% for the ascending aorta in diastole to 0.36% for the ascending aorta in systole. The mean percentage change of aortic area was 8.3% in the ascending aorta (8).

DISCUSSION

Life expectancy of Marfan patients is substantially reduced by cardiovascular complications. Progressive aortic dilation and/or dissection and rupture are the leading causes of death. Beta-blocker therapy seems to delay aor-

Table 1

Aortic Parameters of Marfan Patients, Family Members, and Healthy Volunteers (HV)

	Marfan Patients (n = 20)	Family Members (n = 15)	HV (n = 14)	ANOVA p value
Systolic pressure (mm Hg)	128 ± 8.6	127 ± 14.7	119 ± 14.8	0.122
Diastolic pressure (mm Hg)	80 ± 6.3	75 ± 10.3	74.5 ± 7.2	0.087
Pulse pressure	47.5 ± 9.2	52 ± 12.8	43.4 ± 10.2	0.105
Systolic Area (cm^2)	7.3 ± 2.3	6.9 ± 1.7	6.1 ± 0.6	0.143
Diastolic area (cm^2)	6.8 ± 2.2	5.8 ± 1.7	5.3 ± 0.9	0.051
Normalized systolic area	3.8 ± 1.0	4.0 ± 0.9	3.6 ± 0.4	0.475
Normalized diastolic area	3.5 ± 1.0	3.4 ± 1.0	3.1 ± 0.5	0.393
Distensibility ($mm\ Hg^{-1}$)	0.0085 ± 0.006*	0.016 ± 0.011*	0.025 ± 0.006*	0.0001

Values are means ± SD.

*Marfan patients vs. family members, Marfan patients vs. healthy volunteers, and family members vs. healthy volunteers; $p < 0.05$.

tic dilation by reducing the systolic aortic pulse pressure and the strain and frequency of left ventricular ejection (13,16). Therefore, to provide an effective treatment in patients affected by Marfan syndrome, aortic involvement must be early and accurately established so that medical treatment can be promptly started.

The defect causing Marfan syndrome has recently been identified as the mutation of a gene (*FBN1*), located on chromosome 15, which encodes fibrillin 1 (17). Fibrillin 1 is a large glycoprotein that is part of microfibrils. Because microfibrils are an important constituent of extracellular matrices in most tissues, fibrillin abnormalities may impair the structural and functional integrity of a variety of tissues where these proteins are a component element (18–20). Fibrillin proteins constitute the scaffolding of the elastic fibers in the tunica media of the arterial wall. Abnormal fibrillin coupled with disorganized elastin leads to abnormalization of the elastic properties of the wall. This alteration is the basis of progressive aortic dilatation observed in Marfan patients.

Noninvasive techniques such as echocardiography and MRI have been used to determine aortic distensibility and stiffness index. By MRI, aortic elastic properties can be investigated with two different methods: the ratio of aortic area change and pulse pressure (distensibility) or the quantification of pulse wave velocity through the ascending and descending aorta (13). Compared with echocardiography, MRI has several advantages: It allows the same aortic site to be used on each occasion, which is important when serial measurements are to be made (21). The use of the bifurcation of the pulmonary artery to align MR images ensures that measurements can be made at the same level on each occasion. In addition, its multiplanar acquisition guarantees that images are taken perpendicularly to the aortic lumen. Furthermore, be-

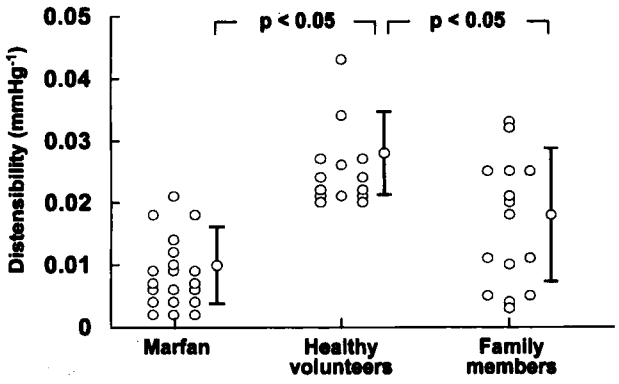

Figure 3. Comparison of aortic distensibility among Marfan patients, family members, and healthy volunteers.

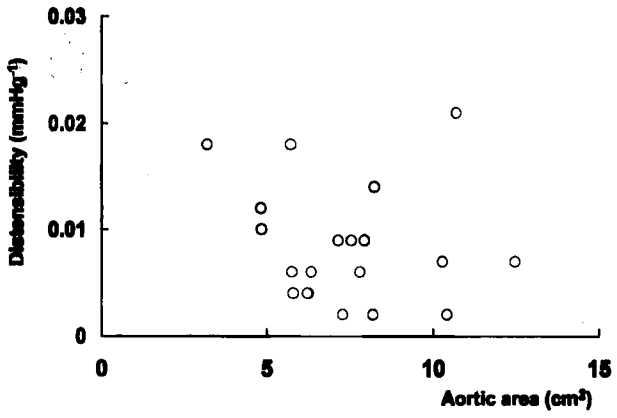

Figure 4. Relationship between aortic distensibility and mid-ascending aortic area in Marfan patients.

cause chest wall deformities are common in Marfan patients, the difficulties in obtaining accurate echocardiogram measurements are increased.

Careful monitoring is suggested for Marfan patients with an aortic diameter of over 4.5 cm, and when the aortic diameter reaches 5.5 cm, prophylactic surgery is recommended. Nevertheless, despite aortic dilation and dissection being strictly related, there is clinical evidence that aortic dissection can also occur in patients with normal aortic diameters (6). For this reason aortic dilation may not be considered a unique and entirely satisfactory criterion in the difficult decision making of preventive surgical strategies (22–25).

Reduced distensibility could be considered a more specific and reliable sign of fibrillin abnormalities, and it could be used as an additional parameter for the timing of aortic replacement. Despite the tendency toward low distensibility in Marfan patients with dilated aorta, in this study no significant correlation was found between aortic dilation and distensibility ($r = -0.16$). Furthermore, as reported in others studies (8), three Marfan patients with dilated ascending aorta presented normal aortic distensibility. The significance of these observations is not yet clear. It is reasonable to suppose that fibrillin abnormalities may be expressed either independently or combined both with aortic dilation and abnormal distensibility (26).

With regard to the family members group, our data revealed abnormal distensibility in seven relatives, four of which presented aortic dimension in the upper limits. Considering the young age of these family members, reduced aortic distensibility might precede the complete expression of aortic involvement, suggesting the time to begin beta-blocker therapy.

Additional studies are needed to determine the potential clinical significance of these findings. In Marfan patients a significant alteration of aorta elasticity may indicate a high risk of dissection or may be an additional parameter to consider in the controversial surgical management. In young family members this may support the suspicion of the syndrome and give rise to a genetic study. Timely diagnosis and treatment represent the only chance to delay the unfavorable outcome of the disease.

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